Perinephric Infection

1 patient suffered a complication which was attributed to perinephric infection. He was a child, aged 7, with severe nephrotic syndrome and moderate azotæmia due to type-I nephritis, and underwent right renal biopsy without incident. Culture of the washings from the biopsy needle was sterile, but coliform organisms were found in the first midstream urine after biopsy. He was given a seven-day course of sulphonamides to which the organisms were sensitive; at the same time (forty-eight hours after biopsy) prednisone therapy was begun. There was no improvement in the nephrotic syndrome, but there were no complaints referable to the biopsy. Two weeks later he suddenly complained of pain in the right loin, and became extremely tender there and on the right side of the abdomen. His temperature rose to 100°F, and a leucocytosis of 18,000 per c.mm. developed over the next twenty-four hours. Urine culture was sterile. He was treated with erythromycin and furaltadone, and made a satisfactory recovery.

Pain

Slight aching in the loin, usually at the biopsy site, and commonly related to movement, was often present in the first twenty-four hours. 5 patients had more severe pain during or after biopsy. 1 adult complained of loin discomfort for three days after biopsy, and another had fairly severe pain immediately after the procedure, which gradually subsided over the next four days. Both were tender over the affected kidney and, although tomograms showed no evidence of large extravasation, it was thought that a small subcapsular hæmatoma might be responsible for the pain. Kark et al. (1958) commented that relatively small subcapsular and perinephric hæmatoma could cause quite severe discomfort.

A child, with relapsing nephritis and probable Henoch's purpura, had discomfort in the loin in the first twenty-four hours after biopsy; and, five days later, a further attack of loin pain associated with slight hæmaturia. In view of the time interval, the second attack may have been due to a flare-up of the illness following biopsy.

A child with nephrotic syndrome and azotæmia, in whom biopsy material was obtained with difficulty, had pain in the right loin and iliac fossa for two days afterwards. There was guarding and rebound tenderness over the right side of the abdomen, but no fever or leucocytosis, and the condition cleared up spontaneously. It was thought that, on the initial insertion, the biopsy needle had passed below the lower pole of the kidney and may have produced a small amount of peritoneal bleeding. There was no fall in hæmoglobin level.

A 5th patient suffered some loin pain in association with urinary infection after biopsy.

Flare-up of Original Disease

In addition to the child with nephritis 2 patients had an obvious exacerbation of their illness after biopsy. A child of 14 with nephrotic syndrome was treated by bed rest and diet for one week after admission, and proteinuria fell from 15 g. per litre to almost zero. The day after biopsy there was no hæmaturia but urinary protein excretion rose again to 12 g. per litre. It fell back to zero during a course of corticotrophin (A.C.T.H.) started forty-eight hours after biopsy. The specimen showed fairly severe thickening of basement membranes (type-I nephritis).

A woman of 45 with a history of recurrent loin pain and frequency had intermittently positive urinary cultures. After biopsy, her urine became heavily infected with organisms similar to those in her last positive culture, and she developed typical symptoms of a urinary infection. This cleared up with antibiotic therapy and she has remained well since.

Biopsy of Wrong Organ

Accidental biopsy of some organ other than the kidney is not uncommon error but one which did not occur in the present series. One biopsy of kidney also contained a tiny fragment of duodenum, and another biopsy included a portion of myocalyx muscle. Neither patient appeared to suffer any harm, which is interesting in view of Kark's conclusion that biopsy of the myocalyx might be responsible for pain at the time of biopsy. This patient was carefully questioned; but had felt no pain whatever after the procedure.

Comparison of the incidence of complications in different series is of questionable value since so much depends on the observer's opinion of, for instance, where mild discomfort ends and pain begins. However, the incidence of uncomfortable complications in this small series (12%) is reasonably close to that in Kark's much larger one (10%).

Summary

A technique of renal biopsy is described which employs a modified Menghini needle and in which the position of the kidney is determined, when possible, by pyelography at the time of biopsy. The results of 50 biopsy attempts are reported.

In this series the success-rate is higher than with the standard method, using the Vim-Silverman needle. The incidence of complications is similar.

The specimens obtained by the present method contain a higher proportion of renal cortex than those taken with a Vim-Silverman needle, and are therefore more useful to the histologist.

I am indebted to Dr. Charles Warwick and Miss J. Young, and their colleagues, for valued cooperation in the radiological department; to Prof. George Smart for advice and encouragement; and to the physicians who kindly allowed access to patients under their care—Prof. George Smart, Prof. S. D. M. Court, Dr. A. G. Ogilvie, Dr. T. H. Boon, Dr. F. J. W. Miller, Dr. G. A. Neligan, and Dr. G. O. Richardson.

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EXPERIMENTAL STAPHYLOCOCCAL INFECTIONS IN MAN

W. D. FOSTER
M.D. Cantab.
LECTURER IN BACTERIOLOGY, ST. THOMAS'S HOSPITAL MEDICAL SCHOOL

M. S. R. HUTT
M.D. Lond., M.R.C.P.
PHYSICIAN TO THE LOUIS JENNER LABORATORY, ST. THOMAS'S HOSPITAL, LONDON, S.E.1

THE earliest attempt to test staphylococcal virulence in man was made by Garré (1885), who rubbed an entire slope culture into the skin of his forearm. This resulted in multiple pustules from which a carbuncle later developed. Since this dramatic demonstration of staphylococcal virulence little experimental work has been performed in man, for obvious reasons. Recently, however, Elek (1956) and Elek and Conen (1957) injected staphylococci intradermally and were able to produce small pustules with doses of over a million organisms; they were unable to produce lesions with killed cocci, and the addition of toxin did not influence the outcome.

In the experiments we describe here we attempted to simulate more closely the conditions obtaining in a wound by using artificial skin lesions into which staphylococci were introduced. By this method we hoped to determine whether local conditions influenced multiplication of organisms or the course of the subsequent lesion, whether different types of staphylococci varied in pathogenicity, and what was the smallest infecting dose.

TABLE I—PHAGE-TYPE AND SOURCE OF *Staph. aureus* USED IN EXPERIMENTS

Phage-type	Source
n.t.	Perineal carrier
n.t.	Nasal carrier
47 77	,, ,,
52 80	,, ,,
3c 55 71*	Septic wound

n.t. = not typable with the routine set of phage.
* = this organism was obtained from an outbreak of wound sepsis (Foster 1960).

Materials and Methods

The strains of staphylococci were isolated on blood-agar and identified by their colonial appearance and slide-coagulase tests. The strains were stored on agar slopes in bijou bottles, and then phage-typed by the method of Anderson and Williams (1956). The phage-type and origin of the various organisms used in these experiments are listed in table I. All were coagulase-positive *Staphylococcus aureus* (with the exception of a coagulase-negative *Staph. albus* used in one experiment), and all were sensitive to the standard antibiotics.

The experimental lesions were made by scraping the epithelium from a small area of skin on the volar surface of the forearm (Rebuck and Yates 1954). Using a scalpel with a small blade, twenty-five strokes were made, this manœuvre resulting in a lesion of constant size which did not bleed, but in the base of which capillary loops were easily visible. The lesions produced in this way were inoculated with a standard platinum loop delivering about 0·005 ml. of an overnight 'Lemco' broth culture containing about 250×10^6 organisms per ml. The standard inoculum was thus approximately 10^6 organisms. The lesions were then sealed with circular flamed coverslips which were held in position with 'Sellotape'.

TABLE II—COMPARISON OF THE MULTIPLICATION OF ORGANISMS IN STANDARD SKIN LESIONS SEALED WITH COVERSLIPS AND LEFT EXPOSED

Time after inoculation	No. of organisms recovered	
	Lesions sealed with coverslips	Lesions allowed to dry
15 min.	$0{\cdot}7 \times 10^6$	$0{\cdot}7 \times 10^6$
2 hours	$1{\cdot}8 \times 10^6$	$0{\cdot}5 \times 10^6$
5 ,,	..	$0{\cdot}4 \times 10^6$
8 ,,	18×10^6	$0{\cdot}8 \times 10^6$
17 ,,	25×10^6	..
27 ,,	55×10^6	$2{\cdot}6 \times 10^6$

Staphylococcal Counts from Skin Lesions

The coverslip and sellotape over each lesion were stripped off and dropped into 10 ml. of nutrient broth in a wide-mouth universal container. One drop of sterile broth was then added to the underlying lesion, and the whole area was thoroughly rubbed with two sterile alginate wool swabs to remove all exudate and superficial layers of the lesion. Both swabs were then broken off into the same sample of nutrient broth as the coverslip. After capping, the universal container was shaken vigorously until the alginate swabs disintegrated.

Serial tenfold dilutions were then prepared in broth using $^1/_{50}$ ml. dropping pipettes, and each dilution was plated out. After overnight incubation the colonies of staphylococci were counted, and from these counts the number recovered from the whole lesion was calculated. In experiments in which coverslips were not used to seal the lesions organism counts were obtained by firm swabbing of the area with alignate swabs after preliminary moistening with broth. The swabs were then dropped into the universal containers as before.

Results

Multiplication of Organisms

Five standard skin lesions were made in two subjects and inoculated as described above with phage-type 3c/55/71. In one subject the lesions were covered with coverslips, and in the other they were left exposed. Counts were then made of the numbers of organisms isolated at various times after inoculation.

It will be seen from table II that the covered lesions showed considerable increase in the numbers of organisms between 2 and 8 hours, followed by a slower increase over the next 14 hours, whereas there was virtually no increase in numbers in the uncovered lesions even after 24 hours. Macroscopically, the covered lesions showed a purulent exudate after a few hours in contrast to the uncovered lesions, which formed a scab with scanty exudate.

Effect of Foreign Material

In view of the possibility that foreign material might influence the results, the effect of rubbing starch and french chalk into the lesions was investigated.

Six standard skin lesions were made and treated as indicated in table III. They were then covered with the lids of small bijou bottles which were strapped on to the arm, keeping the lesions moist but avoiding the direct pressure inevitable with a coverslip. The lesions were left for 24 hours, after which they were inspected and organism-counts were made.

TABLE III—COMPARISON OF ORGANISM-COUNTS AND MACROSCOPIC APPEARANCES IN LESIONS TREATED WITH FOREIGN MATERIAL

Lesion	Appearance at 24 hours	Organism-count at 24 hours	Appearance at 48 hours
1. Control	Serous exudate	0	No erythema
2. Standard loopful of staphs.	Purulent exudate	19×10^6	Erythema +
3. Standard loopful of staphs. – french chalk	,, ,,	17×10^6	,,
4. French chalk ..	Dry lesion	0	No erythema
5. Staphs. – starch ..	Purulent exudate	13×10^6	Erythema +
6. Starch	Slight serous exudate	0	No erythema

The results show no apparent macroscopic difference between the lesions produced in this series and those in which coverslips had been used, although the rate of multiplication of organisms was slower with the bijou-cap method. There was also no significant difference between the lesions to which foreign material had been added and those which were uncontaminated.

Inflammatory Responses in Skin Lesions Infected by Staphylococci

Three skin lesions were made, one of which acted as a control, while the other two were inoculated with a standard loopful of a 24-hour culture of *Staph. albus* or *Staph. aureus* (phage-type 3c/55/71) respectively (table IV). The lesions were then sealed with coverslips, which were changed at intervals during the next 24 hours. The cellular exudate on these coverslips was stained by methylene-blue and examined microscopically. The state of the lesion was recorded after 24 hours.

The essential cytological difference between the infected and the control lesions was the increasing numbers of degenerate polymorphonuclear leucocytes in the infected lesions, whereas

TABLE IV—COMPARISON OF THE INFLAMMATORY RESPONSES IN SKIN LESIONS INFECTED BY *Staph. albus* AND *Staph. aureus*

Time of application of coverslips	Cytology	Control (uninoculated)	*Staph. albus*	*Staph. aureus*
5–8 hours ..	Polymorphs	– –	– –	– –
	Degenerate polymorphs	–	–	+ + +
	Mononuclears	– –	– –	–
	Staphylococci	–	–	– +
9–13 hours ..	Polymorphs	– –	– –	– –
	Degenerate polymorphs	–	– –	– + +
	Mononuclears	– – –	– –	–
	Staphylococci	–	–	+ –
13–24 hours	Polymorphs	– –	– –	+
	Degenerate polymorphs	–	– – –	+ – + +
	Mononuclears	–	–	–
	Staphylococci	–	– –	– – –
Macroscopic appearance at 24 hours (see figure)	..	Serous exudate; no erythema	Seropurulent exudate; no erythema	Purulent exudate surrounding erythema –

– = scanty; – – = moderate number; – – – = numerous.

Comparison of the control skin lesion, C, and lesions inoculated with five different types of *Staph. aureus*.

in the control lesion mononuclear and histiocytic cells increased for 13 hours, when they dominated the picture. Although phagocytosis of organisms by polymorphs was seen on all the coverslips from the infected lesions most organisms were extracellular.

Different Types of aureus and Their Inflammatory Responses

Six standard skin lesions were made; five of these were inoculated with the five different types of *Staph. aureus* listed in table I. The lesions were then sealed with coverslips which were changed at intervals, as already described. After 24 hours all the inoculated lesions showed surrounding erythema and were covered with a purulent exudate, whereas the uninoculated lesion was not erythematous and showed only slight exudate (see figure). There was no essential difference between the lesions produced by the different types of organisms.

Organism Dose and Inflammatory Response

Two sets of five standard lesions were made and inoculated with dilutions of a 24-hour broth culture of *Staph. aureus* (phage-type 3c/55/71). Four of the lesions of one of these sets were inoculated with 100, 1000, 10,000, and 1,000,000 organisms respectively, while the other set was seeded with 240, 120, 60, 30, and 15 organisms. In each set the fifth lesion was inoculated with broth as a control.

The results of the larger dose inoculum are shown in table V. There was little difference between lesions 2, 3, and 4 although the exudate was increased slightly with increasing numbers of organisms. Lesion 5, however, by contrast showed a frankly purulent exudate, and it was indurated and sore. After removal of the coverslips all these lesions dried up and were healed within a week.

The results of the smaller dose inoculum, shown in table VI, indicate that as few as fifteen organisms are sufficient to cause a septic lesion, and they illustrate the rapidity with which the organisms can multiply.

The Staphylococcal Lesions

In the course of these experiments, two of the three subjects developed skin lesions of some severity on the inoculated arm. Soon after inoculation one got a boil and a crop of small pustules in the hairy part of the arm and over the sites of a sellotape reaction; 5 weeks after his last inoculation he developed a further boil in the same area. The organisms from these lesions all belonged to phage-type 3c/55/71. The other subject, who also had some boils on the arm immediately after inoculation, got a large boil on the thigh as well 2 weeks after the last inoculation of organisms. This subject, who had never previously been a nasal carrier of *Staph. aureus*, was at that time found to be carrying phage-type 3c/55/71 in his nose. The boil on his thigh resolved with local treatment, and the nasal carriage was cleared up with a cream containing chlorhexidine and neomycin (' Naseptin '). But 2 weeks later a large abscess developed on the buttock, from which was again grown phage-type 3c/55/71. Before this abscess appeared he had not been a perineal carrier of *Staph. aureus*.

TABLE V—COMPARISON OF ORGANISM-COUNTS AND MACROSCOPIC APPEARANCES OF LESIONS TREATED WITH DIFFERENT DOSES OF *Staph. aureus*

Lesion	Appearance at 24 hours	Organism-count at 24 hours
1. Control	No exudate; no erythema	0
2. 100 organisms	Seropurulent exudate; erythema 5 × 5 mm.	$5{\cdot}2 \times 10^4$
3. 1000 ,,	Seropurulent exudate; erythema 7 × 7 mm.	$8{\cdot}0 \times 10^4$
4. 10,000 ,,	Seropurulent exudate; erythema 7 × 7 mm.	$11{\cdot}0 \times 10^4$
5. 1,000,000 ,,	Purulent exudate; erythema 15 × 15 mm.	$21{\cdot}0 \times 10^4$

Discussion

Despite the extensive reports which have accumulated on the epidemiology of staphylococcal infections, the factors which determine the development of septic lesions in any person remain largely unsolved. Although clinical evidence suggests that certain phage-types of staphylococci are more virulent than others (Barber and Burston 1955), and that passage through a septic lesion also enhances virulence (Beavan and Burry 1956), there is no direct experimental evidence that different strains of *Staph. aureus* differ in virulence. Elek (1956) and Elek and Conen (1957) attempted to test the behaviour of staphylococci in man by injecting them intradermally. They produced small septic lesions with 1–5 million organisms, but were unable to demonstrate any difference in the smallest pus-forming dose between strains obtained from lesions or from healthy nasal carriers and epidemic strains.

TABLE VI—DETERMINATION OF THE SMALLEST INFECTING DOSE

Organisms applied	Organisms recovered at 24 hours	Macroscopic appearances at 24 hours
240	$18{\cdot}5 \times 10^4$	Seropurulent exudate with erythema
120	$10{\cdot}5 \times 10^4$	
60	$11{\cdot}5 \times 10^4$	
30	$11{\cdot}0 \times 10^4$	
15	$6{\cdot}1 \times 10^4$	
0 (broth only)	0	

Using a similar organism dose we have shown that it is possible to demonstrate differences in skin reaction between an uninfected lesion, one inoculated with *Staph. aureus*, and one inoculated with *Staph. albus*. The *Staph. albus* lesion was clearly infected in contrast to the control but the inflammatory reaction was less than in the lesion infected by *Staph. aureus*.

In a similar experiment four types of *Staph. aureus* which had not been associated with infections were compared with a strain (phage-type 3c/55/71) known to have caused several infections. It was not possible to differentiate between the macroscopic or microscopic features of these five lesions at the end of 24 hours: all showed a similar purulent exudate with surrounding erythema. These results confirm those of Elek and Conen (1957), who also attempted to differentiate between lesions produced by organisms from carriers, and those from septic lesions, without success.

The multiplication of staphylococci in these standard infected lesions covered with coverslips followed the expected pattern of growth, with a lag phase followed by a phase of rapid multiplication. But in similar experiments in which the lesions remained uncovered after inoculation, multiplication was delayed for 8 hours. It seems probable that keeping the lesion moist was the significant factor since the 24-hour count after a standard inoculation was similar whether the lesions were covered with coverslips,

or with small lids which retained moisture without causing pressure on the lesion. No evidence was forthcoming that the application of foreign material, such as french chalk or starch, which are used in glove powders, influenced the multiplication of organisms or the 24 hours' inflammatory response. Superficial foreign material, however, cannot be compared with deep foreign bodies, such as sutures. The experimental work of Elek and Conen (1957) has shown that sutures have a significant effect in determining a clinical lesion.

In all the initial experiments in our study the organism numbers in the inoculum were mostly of an order similar to those used by Elek (1956), and thus they bore little relation to clinical reality. In our dilution experiments, however, we found that as few as fifteen organisms could still produce significant sepsis in a standard skin lesion, and also that multiplication of organisms was so rapid that the total organism count at 24 hours was not much different from those infected with larger inocula. In so far as these experimental skin lesions simulated operation wounds, the results indicate that wound infection could also develop after initial contamination with small numbers of organisms. The significance of this finding is enhanced by the observation of Foster (1960), who demonstrated the deposition of occasional staphylococci on an artificial operation site by a carrier using full aseptic technique.

The unplanned subsequent septic lesions in two experimental subjects curtailed further experiments, but illustrated some additional aspects of the behaviour of *Staph. aureus* in the body. The boils on the arms were not necessarily at the site of inoculation but were always centred on hair follicles. These findings are in line with clinical experience and with the experimental work of Bockhart (1887), who excised experimentally produced furuncles and showed histologically that the organisms had multiplied in hair follicles. It may be of significance in this connection that of the three subjects of this experiment the one who escaped infection entirely was a woman, and the one most severely affected was the most hirsute. This subject, who later became a nasal carrier and developed abscesses on the thigh and buttock, illustrates the propensity of the *Staph. aureus* to spread all over the body from an initial infective site, and the importance of separating such infected individuals from the neighbourhood of uninfected healing wounds.

Summary

Artificial skin lesions produced in man were inoculated with staphylococci. Organisms multiplied rapidly if the lesions were kept covered. There was a difference between the inflammatory response produced by *Staphylococcus albus* and *Staph. aureus*, but no evidence that different types of *Staph. aureus* varied in their virulence.

The addition of superficial foreign material did not affect the eventual lesion. Multiplication of organisms with the production of a septic lesion could be produced by as few as fifteen organisms.

The experiments had to be terminated because of the development of other septic lesions in two of the subjects.

Our thanks are due to Dr. E. H. Letchner who volunteered to take part in one experiment and to Prof. Ronald Hare for helpful criticism.

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"BURNING LIPS" ASSOCIATED WITH ŒSOPHAGEAL REFLUX

MAURICE GARRETTS
M.B. Lond., M.R.C.P.
SENIOR REGISTRAR, DEPARTMENT OF DERMATOLOGY, UNIVERSITY COLLEGE HOSPITAL, LONDON, W.C.1

BECAUSE of the unusual presentation, three cases in which œsophageal reflux was shown radiographically are reported.

Case-records

Case 1.—A man, aged 60, employed in a wallpaper factory, complained that for the previous two years he had been constantly troubled by a burning sensation of the tongue, lips, and inside of the mouth generally; this had been worse for the past nine months. He had had colitis, but the last attack was five years ago. He admitted that for many years he had "brought up a lot of wind", especially after meals. He said that he could taste food long after a meal had been taken, and that he had a foul taste in his mouth for most of the day.

The lips appeared normal. The whole of the buccal mucosa was reddened, but the reddening was less intense over the surface of the hard palate under the upper dental plate.

The patient was sure that his dentures had nothing to do with the condition since it had failed to improve when he left them out for several weeks. Patch tests, using denture materials, were negative. Hydrocortisone preparations applied locally to the buccal mucosa, sedatives, and injections of 'Parentrovite' had no effect on the condition. He was not anæmic. Because he worked in a wallpaper factory, his urine was examined for excessive amounts of arsenic, which, however, were not found.

Despite the absence of pain in the chest or the abdomen, the acid taste in his mouth, together with eructations of copious wind, might have been due to a lesion of his œsophagus. A barium swallow showed a sliding hiatus hernia. There was free reflux. Some coarsening of the mucosal folds, compatible with œsophagitis, was seen in the lower œsophagus. No abnormality was demonstrated radiographically in the stomach or duodenum.

He was advised to sleep propped well up on pillows to reduce nocturnal reflux, and to take 'Nulacin' tablets regularly; but, despite several months of medical treatment, the symptoms have persisted. Œsophagoscopic examination is to be made, and, if necessary, the hiatus hernia will be treated surgically.

Case 2.—A man, aged 52, complained of recurrent swellings of the lower lip, together with a burning sensation, and sometimes blistering and superficial ulceration of the lower lip for the past seven months. He said he had a most "foul and disgusting" taste in his mouth, particularly in the mornings. For many years he often had to rise at night and wash out his mouth because of the "dreadful acid taste."

No blistering was seen, but there was some superficial denudation, resembling aphthæ, of the buccal surface of the lower lip. There was no erythema of the buccal mucosa, which was perfectly normal in all other areas. Leaving his dentures out for six weeks had no effect. There was no association with any particular food or drink. Just before the onset of the condition, he had fallen down stairs; and, after this accident, he had a pain in his neck. Because of this pain, he was unable to tolerate his usual number of pillows in bed, and had developed the habit of lying flat.

Barium meal showed that there was no hiatus hernia; but, with the patient in the Trendelenburg position, barium was regurgitated into the lower œsophagus.

In this case the newly acquired habit of sleeping flat seems to have been responsible for the onset of the burning sensation and for the superficial ulceration of the lower lip. He was advised to raise the head of his bed on blocks.

Case 3.—A woman, aged 65, complained of a metallic taste in the mouth for the past six months. She also complained that her tongue was sore, and that she was troubled by soreness of the lips associated with small painful erosions on the buccal